REMARKS

Claims 82 and 85-92 presently appear in this case. No claims have been allowed. The Official Action of November 23, 2010, has now been carefully studied. Reconsideration and allowance are hereby respectfully urged.

Briefly, the present invention relates to a method for the treatment of an ear disorder in a subject in need of such treatment. The treatment comprises administering into the ear canal of the subject a pharmaceutical agent known to affect an ear disorder, in the form of a foam or a mousse. The administration is made by ejecting the foam or mousse into the ear canal from a dispensing device that includes a container and a pipe. The pipe extends from the container and allows access of the foam or mousse into the ear canal. The invention is also directed to such a dispensing device that includes a container containing the medicament in such a manner that, when the medication formulation is dispensed from the container, it is dispensed in the form of a foam or a mousse. The device also includes a pipe that extends at a right angle from the container and that allows access of the foam or mousse to the ear.

The interview graciously granted between examiner Haghighatian and the undersigned attorney on March 30, 2011, is hereby gratefully acknowledged. At this interview, a sample of applicant's product was demonstrated, and a sample of the prior art CORTIFOAM product was shown to the examiner. It was pointed out that while the CORTIFOAM product had a little nose that could be used to fill the manual dispenser, this was not a pipe that extends from the container and allows access of the foam to ear. It was the examiner's position, however, that with respect to a device claim, it does not matter that the CORTIFOAM product is not sold for the purpose of ejecting foam into the ear (or any other body cavity). Furthermore, the examiner considered that the nose on the end could be considered to be the claimed "pipe." Therefore, the examiner stated that she would not withdraw the anticipation rejection over claims 90 and 91 in their present form. The undersigned advised the examiner that, if an RCE were to be filed, claim 90 would be amended to specify that the pipe extended at a right angle from the container, thus avoiding anticipation.

Also at the interview, the method claims were discussed, as were the Purwar, CORTIFOAM, Abram and Klein references cited in the rejections against these claims. The

results established in the Yelin declaration of record were also discussed. The examiner states in the Advisory Action that it was known by persons of ordinary skill in the art that foam provides added contact time for the active agent and as such would be expected to have superior results compared to a solution. The undersigned pointed out at the interview that this statement was not supported by any evidence of record and the examiner was shown numerous pieces of prior art which establish that foam is not expected to be any better than alternative formulations such as liquids, creams, gels and ointments. These publications are submitted herewith and will be discussed below.

The examiner stated in the interview that the results in Study #2 of the Yelin declaration contradict the results in Study #1, which show that the foam is no better than the ear drops. The undersigned explained, however, that Study #1, as set forth in Marom 2010, was not intended to be a showing of superiority but only a showing that substituting equal amounts of medicament in a foam in the same dosage protocol will not be inferior to ear drops. This was shown in Study #1 and, indeed, for many of the end points, the foam was even better than the ear drops. Study #2 was intended to go on to make a comparison to find out if the frequency of administration could be reduced when the foam was used, without losing the effectiveness. It was in the second study that it was unexpectedly found out that the foam was better than the ear drops because the frequency of administration could be cut in half, thus effectively meaning that half the amount of medicament provided the same results. These results do not contradict the results of the first experiment but merely go on to prove that while foam is not inferior to ear drops when using the same administration protocol, they are also as good as ear drops when using half the frequency, meaning half the amount of medicament.

After reviewing the claims, the examiner stated that if applicants were to combine claims 82-84, such a claim would have a better chance of convincing her of patentability over the prior art, particularly in viewing of the showings of record. Accordingly, the present amendment amends claim 82 so as to combine it with the subject matter of claims 83 and 84. Newly amended claim 82 is now effectively claim 84 rewritten into independent form. The examiner also said that if the once a day dosage administration scheme of claim 89 were inserted into claim 82, this would also be very helpful in establish unobviousness. Accordingly, new claim 92 has now been submitted to include this feature. This claim should certainly be allowable, but it is believed that claim 82 should also be

allowable without the necessity of specifying the dosage frequency, for the reasons that will be explained in detail below.

The examiner concluded the interview by stating that if applicant presented the evidence discussed at the interview as part of a submission with an RCE, she would carefully reconsider her position. The present supplemental amendment is being filed as a result of this interview.

All of the obviousness rejections of record seek to establish that it would have been *prima facie* obvious to administer medication to the ear in any of the dosage forms known for other parts of the body, including foam. Indeed the examiner referred to a quotation from a recent Supreme Court case stating that "when an application simply arranges old elements with each performing the same function it had been known to perform and yields no more than one would expect from such an arrangement, the combination is obvious." The examiner further quotes the statement that the relevant question for obviousness is "whether the improvement is more than the predictable use of prior art elements according to their established functions." Thus, it is apparent that the examiner considered the substitution of foam for the liquid, cream or ointment of the secondary references, would have been a simple rearrangement of parts or substitution of equivalents and thus *prima facie* obvious.

However, as is stated in the quotation used by the examiner, the relevant question is whether the improvement is more than the predictable use of prior art elements according to their established functions and whether the combination yields more than one would expect from such an arrangement.

There is nothing in the references applied by the examiner that would suggest that one would obtain better results using foam than using alternative pharmaceutical forms. Note, for example, in Klein, conventional pharmaceutical forms are listed at column 2, lines 59-63 and at column 6, lines 3-11. There is no suggestion that any one of those forms is better than any of the others. Foam is used as the pharmaceutical form in Example II, but liquid is used in Example I and a cream is used in Example III. There is no suggestion anywhere in Klein that any of those three dosage forms is better than any other.

Abram is directed to a mousse composition that has the same enhanced topical delivery as the prior art topical lotions and creams. See column 1, lines 20-34 and lines 60-

65. There is certainly no suggestion therein that the mousse composition of Abram is any more effective than the prior art topical lotions and creams.

The CORTIFOAM product information is completely silent about whether or not the foam composition thereof is any better than a standard enema for the same purpose.

Totally contrary to any expectation raised by the prior art used in the rejections of record, the Yelin declaration of record establishes that, when used in the ear, administration of the medication by foam, as opposed to the conventional ear drops, provides substantial and unexpected advantages. The study #1 reported by Dr. Yelin was a clinical study for assessing safety, efficacy and bioequivalence of an otic foam formulation of ciprofloxacin in comparison to commercial ciprofloxacin ear drops. Study #1 was reported in the Marom 2010 publication. Note that the last paragraph of the first column on page 494 of that publication states that "the primary end point of the clinical response was used to demonstrate the bioequivalence between the two drugs." Furthermore, in the first full paragraph of the first column on page 498, the publication states:

> In this study, both treatments were found to be highly efficacious in achieving cure, thus exhibiting the non-inferiority of the foam-based formulation. [emphasis added]

Accordingly, it is clear that the first study was not intended to show the superiority of the foam based product but only to show bioequivalence to an accepted and approved dosage mode, i.e., the ear drops. Note in the first paragraph of the discussion section on page 497, the publication states:

> The study was not based on a comparison of two entirely different preparations, as was done in other studies. Instead, we compared the same antibiotic agent in two different dosage forms, that is, drops versus foam.

Explicitly, the results showed that the foam was not inferior to the drops.

The second study was designed to investigate whether there was clinical superiority in administration by foam as opposed to the conventional ear drops. More specifically, as set forth in the first sentence of Exhibit B to the Yelin declaration, the objective of the study "was to asses whether a single daily application of the foam formulation provides equivalent therapeutic effect in the treatment of acute diffuse Otitis Externa, as the approved dose of Ciloxan ear drops (applied twice a day)." Exhibit B concludes that the clinical tests demonstrate "that only 7 doses of Foam formulation are

sufficient to cure Otitis externa, while 14 doses are required when using ear drops containing the same antibiotic, at the same level." This proves that the foam formulation is twice as effective as the conventional ear drops as it requires only half of the amount of antibiotic to obtain the desired therapeutic effect while reducing two-fold the potential side effects of the antibiotic.

This proof of clinical superiority for the foam is not inconsistent with the results of the first test, which were not intended to show superiority but only non-inferiority. Accordingly, the examiner's statement at the interview that the first study, as set forth in the Marom publication, is inconsistent with the results in the second study misses the mark. The results of the two studies are not inconsistent and, taken together, the two studies show that foam is not only as good as, but better than the prior art conventional ear drop formulation, using the same antibiotic in the same amount for each dose administered.

Additionally, there are indications of superiority of the foam over the ear drops even in the results set forth in the Marom paper. For example, reference is made to Table 2 on page 496 of the Marom paper. Under "clinical response," there was resolution of the condition in 86.2% of the patients receiving the foam-based ciprofloxacin, but only 78.6% with the solution-based ciprofloxacin. Furthermore, reference is made to the last paragraph of the text on page 496, relating to otic discharge. There it states that, although otorrhea was more frequent in the foam-based ciprofloxacin group than in the solution-based ciprofloxacin group, it completely ceased in the foam-based ciprofloxacin group (100%) but was not completely resolved in the solution-based ciprofloxacin group (84.6%), after the completion of the therapeutic course.

Finally, note the first paragraph on page 497, relating to pain relief effect. There, it shows that in visit 2, the fraction of the analgesic responder population (ARP) in the foam-based ciprofloxacin group was greater than the solution-based ciprofloxacin group (73.3% versus 58.3%, respectively).

In summary, these results are as follows:

Clinical Response	FoamOtic Cipro (n=29)	Ciprofloxacin Ear Drops (n=28)
Resolution	86.2 %	78.6 %

Clinical Response	FoamOtic Cipro (n=29)	Ciprofloxacin Ear Drops (n=28)
Resolution of Otic Discharge	100 % (18/18)	84.6% (11/13)
Percentage of Pain responders at Visit 2 (*)	73.3 % (11/15)	58.3 % (7/12)

While the size of the groups may not have been large enough to provide statistical significance, still these indications of clinical superiority cannot be ignored and portend the evidence of clinic superiority obtained in the second clinical study where the dosages were varied to prove that half the amount of ciprofloxacin provides the same relief when administered in the form of a foam as opposed to in the form of ear drops. This is significant evidence of superiority which cannot be easily dismissed.

In the Advisory Action of March 4, 2011, the examiner first stated that she does not dispute applicant's statement that "the Declaration proves that the foam-based formulation application method of the present invention is unexpectedly superior in efficacy as compared to the ear drops of Purwar." Nevertheless, the examiner stated that the argument was not persuasive, stating:

> It is known by the persons of ordinary skill in the art that foam provides added contact time for the active agent and as such would be expected to have superior results compared to a solution. It would have been obvious to one of ordinary skill in the art to have prepared the formulations of Purwar et al. for treating disorders of the ear in the form of a foam as taught by CORTIFOAM and Abram et al. which would have resulted in a more efficient treatment.

The above-quoted statement of the examiner is not supported by any evidence of record. There is absolutely nothing in the record that would suggest that administration of medicament in the form of a foam would have superior results compared to a solution. This is certainly not taught or suggested by CORTIFOAM or Abram, as discussed above. There is

nothing in either of those references that would suggest to one of ordinary skill in the art that a foam would be superior in any way to a solution. The burden is on the examiner to establish that undisputed evidence of superiority would nonetheless be expected. The examiner has not satisfied this burden by reference to any evidence of record.

Not only is there no evidence of record that foam would be expected to be superior to a solution-based application, as alleged by the examiner, but applicantis aware of substantial evidence that there would be no such expectation. At the interview, applicant pointed to many publications that conclude that superiority in efficacy would not be expected when substituting a foam-based dosage form for a prior art liquid, cream or lotion based dosage form. Copies of each of the publications discussed below are being submitted on even date herewith as part of an Information Disclosure Statement. Thus, the examiner's attention is invited to the conclusions in the following publications, which run counter to the examiner's unsupported allegations that one of ordinary skill in the art would expect foam to have superior results compared to a solution.

Ruddell et al., "Treatment of distal ulcerative colitis (proctosigmoiditis) in relapse: comparison of hydrocordisone enemas and rectal hydrocortisone foam" *Gut*, 21:885-889 (1980) compares traditional aqueous hydrocortisone enemas to a suspension of hydrocortisone in an inert foam base, each treatment containing the same amount of hydrocortisone. The summary states:

> Both agents were effective, and broadly similar in terms of objective improvement, … .

On page 887, Ruddell shows that there was no significant difference in the response between the two treatment groups with respect to diarrhea, urgency and tenesmus. With respect to sigmoidoscopic appearance, there was no significant difference between treatments. When analyzing histology, the paper states on the second column of page 887:

> In the enema group, there was a significant improvement in active inflammation score from 4.4 ± 0.5 (mean ± SEM) before treatment, to 2.5 ± 0.5 after treatment (t=2.536, $P < 0.05$). In the foam group, the initial active inflammation score was 5.2 ± 0.6 (mean ± SEM) and this changed insignificantly after treatment to 5.9 ± 0.8.

Thus, the enema was better than the foam from the point of view of histology. Clearly, therefore, this publication contradicts the examiner's unsupported conclusion that

CORTIFOAM would be expected by those of ordinary skill in the art to provide superior results as compared to a solution, i.e., the prior art liquid based enema.

In Gross et al. "Budesonide foam versus budesonide enema in active ulcerative proctitis and proctosigmoiditis" *Aliment Pharmacol Ther,* 23:303-312 (2006), the same active ingredient was compared in foam dosage form and in solution dosage form (enema). The conclusion as set forth in the last paragraph of the summary on page 303 is:

> Budesonide foam is effective as Budesonide enema in the treatment of active ulcerative proctitis or proctosigmoiditis."

Accordingly, this teaches that the efficacy of the foam is no better than the efficacy of the solution, contrary to the examiner's statement. Note further the primary efficacy evaluation section, beginning on page 306 of Gross, which reports that the clinical remission rates were 60% for foam and 66% for enema. Similarly, in the ITT analysis the remission rates were 57% for foam and 65% for enema (second column on page 306 of Gross). Both of these figures show that the foam is not quite as good as the enema. Similarly, in the secondary efficacy evaluation on page 307, the paper states that the rates for endoscopic remission were 52% for budesonide foam and 54% for budesonide enema and that the therapeutic success rates were 58% for foam and 64% for enema. Thus, this paper effectively confirms the results of the Ruddell paper that a foam dosage form does not provide superior results as compared to a liquid dosage form.

Similarly, reference is made to Cortot et al. "Mesalamine foam enema vs. mesalamine liquid enema in active left-sided ulcerative colitis" *Am J. Gastroenterol,* 103:3106-3114 (2008). Again, foam was compared to liquid with the same medicine. The conclusions at the end of the abstract begin:

> A 4-wk treatment of 1 g mesalamine foam induced a clinical remission in 68% patients versus 73% with 1 g mesalamine liquid enema.

Note further the statement at the beginning of the last paragraph on page 3112 of Cortot, stating:

> The findings reported here are in good agreement with data in the literature: in most trials, clinical and endoscopic remission with mesalamine foam enema are close to that achieved with liquid enema, endoscopic remission being 10% somewhat lower with both formulations.

Similar results were demonstrated in Ardizzone et al. "Mesalazine foam (Salofalk foam) in the treatment of active distal ulcerative colitis: A comparative trial vs. Salofalk enema: The SAF-3 study group" *Ital J. Gastroenterol Hepatol,* 31:677-84 (1999), which concludes that Salofalk foam and enema are equally effective for the treatment of proctitis, proctosigmoiditis and left-sided ulcerative colitis. The foam is disclosed as an alternative to the solution-based enema, but there is no disclosure that the foam is better than the liquid enema. Indeed, remission was achieved in only 54% of patients treated with foam and 67% of those treated with enema.

The abstract of Woodford and Barry "Bioavailability and activity of topical corticosteroids from a novel drug delivery system, the aerosol quick-break foam" *J. Pharm Sci,* 66:99-103 (1977), states that the activities of betamethasone benzoate concentrate, collapsed foam, ointment and gel were all similar.

In Borelli et al., "Cream or foam in pedal skin care: towards the ideal vehicle for urea used against dry skin," *Int. J. Cosmet Sci* 33:37-43 (2011), it was reported that the urea-containing cream formulation appeared equal or slightly superior to the foam formulation. It concludes, after comparing the cream and the foam:

> At present, it looks as if cream vehicles would still be vehicles of choice in general, when it comes to the formulation of skin care preparations for not only dry skin but also in the context of pedal skin care."

The abstract in Franz et al., "Bioavailability of clobetasol propionate in different vehicles," *Skin Pharmacol Appl Skin Physiol*, 16(4):212-216 (2003) compares the relative bioavailability of clobetasol propionate from Skin Cap to two FDA-approved formulations of clobetasol propionate (Olux foam and Temovate scalp application). The abstract concludes that there was no significant difference in the percutaneous absorption of clobetasol propionate among the various dosage forms when applied under occluded conditions.

Lucidarme et al., "Efficacy and tolerance of mesalazine suppositories vs. hydrocortisone foam in proctitis" *Aliment Pharmacol Ther,* 11(2):335-340 (1997) reports that mesalazine suppositories were as well tolerated as hydrocortisone foam but were more effective for some parameters of disease activity.

Similarly, Farup et al. "Mesalazine suppositories versus hydrocortisone foam in patients with distal ulcerative colitis. A comparison of the efficacy and practicality of two topical treatment regimens," *Scand J. Gastroenterol,* 30(2):164-170 (1995) also reports that while both treatment regimens are effective, mesalazine suppositories seem to be the preferred alternative to the hydrocortisone foam.

Tarpila et al., "Budesonide enema in active haemorrhagic proctitis –- a controlled trial against hydrocortisone foam enema," *Aliment Pharmacol Ther,* 8(6):591-595 (1994) concludes that budesonide enema is as effective as hydrocortisone foam enema but without the potential for side-effects associated with suppression of plasma cortisol.

Similarly, Ngo and Rambaud "[5-aminosalycilic acid enema (Pentasa) versus hydrocortisone acetate foam (Proctocort) for the treatment of outbreaks of proctitis and cryptogenetic proctosigmoiditis. A comparative randomized multicentered trial]," *Gastroenterol Clin Biol,* 16(6-7):558-563 (1992) reports that after two weeks, 5-amino salicylic acid enemas are more effective than hydrocortisone foam for topical treatment with idiopathic proctitis or proctosigmoiditis.

Somerville et al., "Effect of treatment on symptoms and quality of life in patients with ulcerative colitis: comparative trial of hydrocortisone acetate foam and prednisolone 21-phosphate enemas," *British Medical Journal,* 291:866 (1985), reports:

> Treatments were equally effective in reducing bowel frequency, urgency, incontinence, and lassitude, but tenesmus was more completely alleviated at two weeks in those receiving the prednisolone enemas .... Sigmoidoscopic abnormalities improved similarly in both groups. After two weeks of treatment, four patients changed from the foam to the enema because of poor response ....

In addition to all of these published reports contradicting the unsupported statement of the examiner, applicants have made a study of FDA approved products for the same active ingredient but different dosage forms when one of those dosage forms is foam. Attached hereto is a table containing the results of that research. In no case is the FDA approved dose regime for the foam less frequent than the dose regime for the alternative dosage form, whether liquid gel or cream. Furthermore, there is no indication that the dosage size can be less for the foam than the cream.

Accordingly, this FDA-derived information also supports the conclusion that one of ordinary skill in the art, who had not read the present specification, would not conclude that foam would be expected to have superior results compared to a solution. Thus, it is urged that the data of record, considered in conjunction with the expectations of the art, clearly establishes that the improved results are unexpected and rebut any *prima facie* case of obviousness. Reconsideration and withdrawal of all of the rejections of the method claims are therefore respectfully urged.

With respect to the product claims, claims 91 and 92 have now been amended to specify that the pipe is at a right angle to the container, as is clearly shown in the figures of both the present application and the priority application. This is not the case with CORTIFOAM and there would be no reason why one of ordinary skill in the art would change the orientation of the nose of the CORTIFOAM container, which is only used for filling an applicator and not for application to the body. Accordingly, the presently amended claims are not anticipated by CORTIFOAM. Reconsideration and withdrawal of this rejection is also respectfully urged.

It is submitted that all of the claims now present in the case clearly define over the references of record and fully comply with 35 USC 112. Reconsideration and allowance are therefore earnestly solicited.

Respectfully submitted,

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